

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Philip John Burke and Richard John Knox

Serial No.: Continuation of 09/445,865

Express Mail Label  
No. EL 778 572 141 US

Filed: March 13, 2002

Date of Deposit: March 13, 2002

For: THERAPEUTIC SYSTEMS

Box Patent Application  
Commissioner of Patents and Trademarks  
Washington, D.C. 20231

**PRELIMINARY AMENDMENT**

Sir:

Prior to examination, please amend the application as follows:

**In the Specification**

On page 1, after the title and before the first paragraph, please add the following heading and paragraph.

**--CROSS-REFERENCE TO RELATED APPLICATIONS**

This application is a continuation of pending prior application Serial No. 09/445,865 filed February 11, 2000, entitled "*Therapeutic Systems*", by Philip John Burke and Richard John Knox, which is a 371 of International Application No. PCT/GB98/01731 filed in the United Kingdom Receiving Office for the Patent Cooperation Treaty on June 15, 1998, which claims priority to British application No. GB9712370.7 filed on June 14, 1997.--

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### **In the Abstract**

Please insert the following Abstract as page 89 after the claims and before the drawings.

#### **--Abstract**

A compound comprising a target cell-specific portion and human NAD(P)H:quinone reductase 2 (NQO2) or a variant or fragment or fusion or derivative thereof which has substantially the same activity as NQO2 towards a given prodrug, or a polynucleotide encoding said NQO2 or said variant or fragment or fusion or derivative. A recombinant polynucleotide comprising a target cell-specific promoter operably linked to a polynucleotide encoding human NAD(P)H:quinone reductase 2 (NQO2) or a variant or fragment or fusion or derivative thereof which has substantially the same activity as NQO2 towards a given prodrug. The compounds and polynucleotides are useful in a method of treating a patient in conjunction with a suitable prodrug. A method of treating a human patient with a target cell to be destroyed wherein the target cell expresses NQO2 the method comprising administering to the patient a prodrug which is converted to a substantially cytotoxic drug by the action of NQO2 and nicotinamide riboside (reduced) (NRH) or an analogue thereof which can pass reducing equivalents to NQO2.--

### **In the Claims**

2. (Amended) A compound according to [C]claim 1 comprising a target cell-specific portion and human NAD(P)H:quinone reductase 2 (NQO2).
3. (Amended) A compound according to [Claim 1 or 2] claim 1 wherein the target cell-specific portion is tumour cell-specific.

4. (Amended) A compound according to [any one of Claims 1 to 3] claim 1 wherein the target cell-specific portion comprises an antibody or fragment or derivative.

5. (Amended) A compound according to [any one of Claims 1 to 3] claim 1 wherein the target cell-specific portion comprises a macromolecule.

6. (Amended) A compound according to [any one of Claims 1 to 5] claim 1 wherein the human NAD(P)H:quinone reductase 2 (NQO2) or a variant or fragment or fusion or derivative thereof is capable of being located substantially inside or following expression of the polynucleotide is located substantially inside the target cell.

7. (Amended) A compound according to [any one of Claims 1 to 6] claim 1 comprising means for delivering said polynucleotide to said target cell.

9. (Amended) A recombinant polynucleotide according to [C]claim 8 wherein said promoter is tumour cell-specific.

10. (Amended) A recombinant polynucleotide according to [C]claim 8 [or 9] comprising a polynucleotide encoding NQO2.

11. (Amended) A recombinant polynucleotide according to [any one of Claims 8 to 10] claim 8 which is capable, following expression in a target cell, of providing the NQO2 or a variant or fragment or fusion or derivative thereof located substantially inside the target cell.

12. (Amended) A compound according to [any one of Claims 1 to 7] claim 1 wherein said polynucleotide is the recombinant polynucleotide of [any one of Claims 8 to 11] claim 8.

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13. (Amended) A therapeutic system comprising a compound according to [any one of Claims 1 to 7 or 12] claim 1, or a polynucleotide according to [any one of Claims 8 to 11] claim 8 and a prodrug which is converted to a substantially cytotoxic drug by the action of NQO2.

14. (Amended) A system according to [C]claim 13 wherein the prodrug is CB 1954 or an analogue thereof.

15. (Amended) A system according to [C]claim 14 wherein the prodrug is CB 1954.

16. (Amended) A system according to [any one of Claims 13 to 15] claim 13 further comprising a cosubstrate for NQO2.

17. (Amended) A system according to [C]claim 16 wherein the cosubstrate is nicotinamide riboside (reduced) (NRH) or an analogue thereof which can pass reducing equivalents to NQO2.

18. (Amended) A method of treating a patient with a target cell to be destroyed the method comprising (a) administering to the patient a compound according to [any one of Claims 1 to 7 or 12] claim 1, or a recombinant polynucleotide according to [any one of Claims 8 to 11] claim 8; (b) allowing the NQO2 or a variant or fragment or fusion or derivative thereof to localize at, or be expressed in, the target cell; and (c) administering a prodrug which is converted to a substantially cytotoxic drug by the action of NQO2.

19. (Amended) A method according to [C]claim 18 wherein the patient has a tumour to be treated.

20. (Amended) A method according to [C]claim 18 [or 19] wherein the prodrug is CB 1954 or an analogue thereof.

21. (Amended) A method according to [C]claim 20 wherein the prodrug is CB 1954.

22. (Amended) A method according to [any one of Claims 18 to 21] claim 18 the method further comprising administering to the patient a cosubstrate for NQO2.

23. (Amended) A method according to [C]claim 22 wherein the cosubstrate is nicotinamide riboside (reduced) (NRH) or an analogue thereof which can pass reducing equivalents to NQO2.

24. (Amended) A compound according to [any one of Claims 1 to 7 or 12] claim 1, or a recombinant polynucleotide according to [any one of Claims 8 to 10] claim 8, for use in medicine.

25. (Amended) Use of a compound according to [any one of Claims 1 to 7 or 12] claim 1, or a recombinant polynucleotide according to [any one of Claims 8 to 11] claim 8, in the manufacture of a medicament for treating a patient with a target cell to be destroyed.

26. (Amended) Use as defined in [C]claim 25 wherein the patient has been, is being or will be administered a prodrug which is converted to a substantially cytotoxic drug by the action of NQO2.

27. (Amended) Use of a prodrug which is converted to a substantially cytotoxic drug by the action of NQO2 in the manufacture of a medicament for treating a patient with a target cell to be destroyed wherein the patient has been, is being or will be administered a compound

according to [any one of Claims 1 to 7 or 12] claim 1, or a recombinant polynucleotide according to [any one of Claims 8 to 11] claim 8.

28. (Amended) Use as defined in [C]claim 27 wherein the patient has a tumour to be treated.

30. (Amended) A method according to [C]claim 29 wherein the cytotoxic drug is CB 1954 or an analogue thereof.

31. (Amended) A method according to [C]claim 29 [or 30] wherein the analogue of NRH is able to permeate the target cell membrane.

32. (Amended) A method according to [any one of Claims 29 to 31] claim 29 wherein the target cell is a tumour.

33. (Amended) A method according to [any one of Claims 29 to 32] claim 29 the method further comprising determining, before administering the prodrug or NRH or an analogue thereof, whether the target cell to be treated expresses NQO2.

37. (Amended) Use as defined in [C]claim 36 wherein the patient has been, is being or will be administered a prodrug which is converted to a substantially cytotoxic drug by the action of NQO2.

40. (Amended) [Any novel] The method of [treating] claim 29 wherein the patient has cancer [as herein disclosed].


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### Remarks

Applicants have attached a copy of amended page 1 of the specification pursuant to 37 C.F.R. § 1.121(b)(1)(iii), a clean copy of amended page 1 of the specification pursuant to 37 C.F.R. § 1.121(b)(1)(ii), and a clean copy of the Abstract pursuant to 37 C.F.R. § 1.121(b)(1)(i).

Applicants have included in this Preliminary Amendment a marked-up version of the amended claims pursuant to 37 C.F.R. § 1.121(c)(1)(ii), a clean copy of the amended claims pursuant to 37 C.F.R. § 1.121(c)(1)(i), and a copy of the claims as pending upon entry of the Preliminary Amendment.

Respectfully submitted,

  
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Date: March 13, 2002

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**Marked-Up Version of Amended Claims  
Pursuant to 37 C.F.R. § 1.121(c)(1)(ii)**

2. (Amended) A compound according to [C]claim 1 comprising a target cell-specific portion and human NAD(P)H:quinone reductase 2 (NQO2).
3. (Amended) A compound according to [Claim 1 or 2] claim 1 wherein the target cell-specific portion is tumour cell-specific.
4. (Amended) A compound according to [any one of Claims 1 to 3] claim 1 wherein the target cell-specific portion comprises an antibody or fragment or derivative.
5. (Amended) A compound according to [any one of Claims 1 to 3] claim 1 wherein the target cell-specific portion comprises a macromolecule.
6. (Amended) A compound according to [any one of Claims 1 to 5] claim 1 wherein the human NAD(P)H:quinone reductase 2 (NQO2) or a variant or fragment or fusion or derivative thereof is capable of being located substantially inside or following expression of the polynucleotide is located substantially inside the target cell.
7. (Amended) A compound according to [any one of Claims 1 to 6] claim 1 comprising means for delivering said polynucleotide to said target cell.
9. (Amended) A recombinant polynucleotide according to [C]claim 8 wherein said promoter is tumour cell-specific.
10. (Amended) A recombinant polynucleotide according to [C]claim 8 [or 9] comprising a polynucleotide encoding NQO2.



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11. (Amended) A recombinant polynucleotide according to [any one of Claims 8 to 10] claim 8 which is capable, following expression in a target cell, of providing the NQO2 or a variant or fragment or fusion or derivative thereof located substantially inside the target cell.

12. (Amended) A compound according to [any one of Claims 1 to 7] claim 1 wherein said polynucleotide is the recombinant polynucleotide of [any one of Claims 8 to 11] claim 8.

13. (Amended) A therapeutic system comprising a compound according to [any one of Claims 1 to 7 or 12] claim 1, or a polynucleotide according to [any one of Claims 8 to 11] claim 8 and a prodrug which is converted to a substantially cytotoxic drug by the action of NQO2.

14. (Amended) A system according to [C]claim 13 wherein the prodrug is CB 1954 or an analogue thereof.

15. (Amended) A system according to [C]claim 14 wherein the prodrug is CB 1954.

16. (Amended) A system according to [any one of Claims 13 to 15] claim 13 further comprising a cosubstrate for NQO2.

17. (Amended) A system according to [C]claim 16 wherein the cosubstrate is nicotinamide riboside (reduced) (NRH) or an analogue thereof which can pass reducing equivalents to NQO2.

18. (Amended) A method of treating a patient with a target cell to be destroyed the method comprising (a) administering to the patient a compound according to [any one of Claims 1 to 7 or 12] claim 1, or a recombinant polynucleotide according to [any one of Claims 8 to 11]

claim 8; (b) allowing the NQO2 or a variant or fragment or fusion or derivative thereof to localize at, or be expressed in, the target cell; and (c) administering a prodrug which is converted to a substantially cytotoxic drug by the action of NQO2.

19. (Amended) A method according to [C]claim 18 wherein the patient has a tumour to be treated.

20. (Amended) A method according to [C]claim 18 [or 19] wherein the prodrug is CB 1954 or an analogue thereof.

21. (Amended) A method according to [C]claim 20 wherein the prodrug is CB 1954.

22. (Amended) A method according to [any one of Claims 18 to 21] claim 18 the method further comprising administering to the patient a cosubstrate for NQO2.

23. (Amended) A method according to [C]claim 22 wherein the cosubstrate is nicotinamide riboside (reduced) (NRH) or an analogue thereof which can pass reducing equivalents to NQO2.

24. (Amended) A compound according to [any one of Claims 1 to 7 or 12] claim 1, or a recombinant polynucleotide according to [any one of Claims 8 to 10] claim 8, for use in medicine.

25. (Amended) Use of a compound according to [any one of Claims 1 to 7 or 12] claim 1, or a recombinant polynucleotide according to [any one of Claims 8 to 11] claim 8, in the manufacture of a medicament for treating a patient with a target cell to be destroyed.

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26. (Amended) Use as defined in [C]claim 25 wherein the patient has been, is being or will be administered a prodrug which is converted to a substantially cytotoxic drug by the action of NQO2.

27. (Amended) Use of a prodrug which is converted to a substantially cytotoxic drug by the action of NQO2 in the manufacture of a medicament for treating a patient with a target cell to be destroyed wherein the patient has been, is being or will be administered a compound according to [any one of Claims 1 to 7 or 12] claim 1, or a recombinant polynucleotide according to [any one of Claims 8 to 11] claim 8.

28. (Amended) Use as defined in [C]claim 27 wherein the patient has a tumour to be treated.

30. (Amended) A method according to [C]claim 29 wherein the cytotoxic drug is CB 1954 or an analogue thereof.

31. (Amended) A method according to [C]claim 29 [or 30] wherein the analogue of NRH is able to permeate the target cell membrane.

32. (Amended) A method according to [any one of Claims 29 to 31] claim 29 wherein the target cell is a tumour.

33. (Amended) A method according to [any one of Claims 29 to 32] claim 29 the method further comprising determining, before administering the prodrug or NRH or an analogue thereof, whether the target cell to be treated expresses NQO2.

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37. (Amended) Use as defined in [C]claim 36 wherein the patient has been, is being or will be administered a prodrug which is converted to a substantially cytotoxic drug by the action of NQO2.

40. (Amended) [Any novel] The method of [treating] claim 29 wherein the patient has cancer [as herein disclosed].

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**Clean Copy of Amended Claims  
Pursuant to 37 C.F.R. § 1.121(c)(1)(i)**

2. (Amended) A compound according to claim 1 comprising a target cell-specific portion and human NAD(P)H:quinone reductase 2 (NQO2).
3. (Amended) A compound according to claim 1 wherein the target cell-specific portion is tumour cell-specific.
4. (Amended) A compound according to claim 1 wherein the target cell-specific portion comprises an antibody or fragment or derivative.
5. (Amended) A compound according to claim 1 wherein the target cell-specific portion comprises a macromolecule.
6. (Amended) A compound according to claim 1 wherein the human NAD(P)H:quinone reductase 2 (NQO2) or a variant or fragment or fusion or derivative thereof is capable of being located substantially inside or following expression of the polynucleotide is located substantially inside the target cell.
7. (Amended) A compound according to claim 1 comprising means for delivering said polynucleotide to said target cell.
9. (Amended) A recombinant polynucleotide according to claim 8 wherein said promoter is tumour cell-specific.
10. (Amended) A recombinant polynucleotide according to claim 8 comprising a polynucleotide encoding NQO2.

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11. (Amended) A recombinant polynucleotide according to claim 8 which is capable, following expression in a target cell, of providing the NQO2 or a variant or fragment or fusion or derivative thereof located substantially inside the target cell.

12. (Amended) A compound according to claim 1 wherein said polynucleotide is the recombinant polynucleotide of claim 8.

13. (Amended) A therapeutic system comprising a compound according to claim 1, or a polynucleotide according to claim 8 and a prodrug which is converted to a substantially cytotoxic drug by the action of NQO2.

14. (Amended) A system according to claim 13 wherein the prodrug is CB 1954 or an analogue thereof.

15. (Amended) A system according to claim 14 wherein the prodrug is CB 1954.

16. (Amended) A system according to claim 13 further comprising a cosubstrate for NQO2.

17. (Amended) A system according to claim 16 wherein the cosubstrate is nicotinamide riboside (reduced) (NRH) or an analogue thereof which can pass reducing equivalents to NQO2.

18. (Amended) A method of treating a patient with a target cell to be destroyed the method comprising (a) administering to the patient a compound according to claim 1, or a recombinant polynucleotide according to claim 8; (b) allowing the NQO2 or a variant or fragment or fusion or derivative thereof to localize at, or be expressed in, the target cell; and (c)

administering a prodrug which is converted to a substantially cytotoxic drug by the action of NQO2.

19. (Amended) A method according to claim 18 wherein the patient has a tumour to be treated.

20. (Amended) A method according to claim 18 wherein the prodrug is CB 1954 or an analogue thereof.

21. (Amended) A method according to claim 20 wherein the prodrug is CB 1954.

22. (Amended) A method according to claim 18 the method further comprising administering to the patient a cosubstrate for NQO2.

23. (Amended) A method according to claim 22 wherein the cosubstrate is nicotinamide riboside (reduced) (NRH) or an analogue thereof which can pass reducing equivalents to NQO2.

24. (Amended) A compound according to claim 1, or a recombinant polynucleotide according to claim 8, for use in medicine.

25. (Amended) Use of a compound according to claim 1, or a recombinant polynucleotide according to claim 8, in the manufacture of a medicament for treating a patient with a target cell to be destroyed.

26. (Amended) Use as defined in claim 25 wherein the patient has been, is being or will be administered a prodrug which is converted to a substantially cytotoxic drug by the action of NQO2.

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27. (Amended) Use of a prodrug which is converted to a substantially cytotoxic drug by the action of NQO2 in the manufacture of a medicament for treating a patient with a target cell to be destroyed wherein the patient has been, is being or will be administered a compound according to claim 1, or a recombinant polynucleotide according to claim 8.

28. (Amended) Use as defined in claim 27 wherein the patient has a tumour to be treated.

30. (Amended) A method according to claim 29 wherein the cytotoxic drug is CB 1954 or an analogue thereof.

31. (Amended) A method according to claim 29 wherein the analogue of NRH is able to permeate the target cell membrane.

32. (Amended) A method according to claim 29 wherein the target cell is a tumour.

33. (Amended) A method according to claim 29 the method further comprising determining, before administering the prodrug or NRH or an analogue thereof, whether the target cell to be treated expresses NQO2.

37. (Amended) Use as defined in claim 36 wherein the patient has been, is being or will be administered a prodrug which is converted to a substantially cytotoxic drug by the action of NQO2.

40. (Amended) The method of claim 29 wherein the patient has cancer.



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*Claims As Pending Upon Entry of Preliminary Amendment*

1. A compound comprising a target cell-specific portion and human NAD(P)H:quinone reductase 2 (NQO2) or a variant or fragment or fusion or derivative thereof which has substantially the same activity as NQO2 towards a given prodrug, or a polynucleotide encoding said NQO2 or said variant or fragment or fusion or derivative.
2. (Amended) A compound according to claim 1 comprising a target cell-specific portion and human NAD(P)H:quinone reductase 2 (NQO2).
3. (Amended) A compound according to claim 1 wherein the target cell-specific portion is tumour cell-specific.
4. (Amended) A compound according to claim 1 wherein the target cell-specific portion comprises an antibody or fragment or derivative.
5. (Amended) A compound according to claim 1 wherein the target cell-specific portion comprises a macromolecule.
6. (Amended) A compound according to claim 1 wherein the human NAD(P)H:quinone reductase 2 (NQO2) or a variant or fragment or fusion or derivative thereof is capable of being located substantially inside or following expression of the polynucleotide is located substantially inside the target cell.
7. (Amended) A compound according to claim 1 comprising means for delivering said polynucleotide to said target cell.

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8. A recombinant polynucleotide comprising a target cell-specific promoter operably linked to a polynucleotide encoding human NAD(P)(H):quinone reductase 2 (NQO2) or a variant or fragment or fusion or derivative thereof which has substantially the same activity as NQO2 towards a given prodrug.

9. (Amended) A recombinant polynucleotide according to claim 8 wherein said promoter is tumour cell-specific.

10. (Amended) A recombinant polynucleotide according to claim 8 comprising a polynucleotide encoding NQO2.

11. (Amended) A recombinant polynucleotide according to claim 8 which is capable, following expression in a target cell, of providing the NQO2 or a variant or fragment or fusion or derivative thereof located substantially inside the target cell.

12. (Amended) A compound according to claim 1 wherein said polynucleotide is the recombinant polynucleotide of claim 8.

13. (Amended) A therapeutic system comprising a compound according to claim 1, or a polynucleotide according to claim 8 and a prodrug which is converted to a substantially cytotoxic drug by the action of NQO2.

14. (Amended) A system according to claim 13 wherein the prodrug is CB 1954 or an analogue thereof.

15. (Amended) A system according to claim 14 wherein the prodrug is CB 1954.

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16. (Amended) A system according to claim 13 further comprising a cosubstrate for NQO2.

17. (Amended) A system according to claim 16 wherein the cosubstrate is nicotinamide riboside (reduced) (NRH) or an analogue thereof which can pass reducing equivalents to NQO2.

18. (Amended) A method of treating a patient with a target cell to be destroyed the method comprising (a) administering to the patient a compound according to claim 1, or a recombinant polynucleotide according to claim 8; (b) allowing the NQO2 or a variant or fragment or fusion or derivative thereof to localize at, or be expressed in, the target cell; and (c) administering a prodrug which is converted to a substantially cytotoxic drug by the action of NQO2.

19. (Amended) A method according to claim 18 wherein the patient has a tumour to be treated.

20. (Amended) A method according to claim 18 wherein the prodrug is CB 1954 or an analogue thereof.

21. (Amended) A method according to claim 20 wherein the prodrug is CB 1954.

22. (Amended) A method according to claim 18 the method further comprising administering to the patient a cosubstrate for NQO2.

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23. (Amended) A method according to claim 22 wherein the cosubstrate is nicotinamide riboside (reduced) (NRH) or an analogue thereof which can pass reducing equivalents to NQO2.

24. (Amended) A compound according to claim 1, or a recombinant polynucleotide according to claim 8, for use in medicine.

25. (Amended) Use of a compound according to claim 1, or a recombinant polynucleotide according to claim 8, in the manufacture of a medicament for treating a patient with a target cell to be destroyed.

26. (Amended) Use as defined in claim 25 wherein the patient has been, is being or will be administered a prodrug which is converted to a substantially cytotoxic drug by the action of NQO2.

27. (Amended) Use of a prodrug which is converted to a substantially cytotoxic drug by the action of NQO2 in the manufacture of a medicament for treating a patient with a target cell to be destroyed wherein the patient has been, is being or will be administered a compound according to claim 1, or a recombinant polynucleotide according to claim 8.

28. (Amended) Use as defined in claim 27 wherein the patient has a tumour to be treated.

29. A method of treating a human patient with a target cell to be destroyed wherein the target cell expresses NQO2 the method comprising administering to the patient a prodrug

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which is converted to a substantially cytotoxic drug by the action of NQO2 and nicotinamide riboside (reduced) (NRH) or an analogue thereof which can pass reducing equivalents to NQO2.

30. (Amended) A method according to claim 29 wherein the cytotoxic drug is CB 1954 or an analogue thereof.

31. (Amended) A method according to claim 29 wherein the analogue of NRH is able to permeate the target cell membrane.

32. (Amended) A method according to claim 29 wherein the target cell is a tumour.

33. (Amended) A method according to claim 29 the method further comprising determining, before administering the prodrug or NRH or an analogue thereof, whether the target cell to be treated expresses NQO2.

34. A therapeutic system comprising a prodrug which is converted to a substantially cytotoxic drug by the action of NQO2 and nicotinamide riboside (reduced) (NRH) or an analogue thereof which can pass reducing equivalents to NQO2.

35. Nicotinamide riboside (reduced) (NRH) or an analogue thereof which can pass reducing equivalents to NQO2 for use in medicine.

36. Use of nicotinamide riboside (reduced) (NRH) or an analogue thereof which can pass reducing equivalents to NQO2 in the manufacture of a medicament for treating a human patient with a target cell to be destroyed.

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37. (Amended) Use as defined in claim 36 wherein the patient has been, is being or will be administered a prodrug which is converted to a substantially cytotoxic drug by the action of NQO2.

38. Use of a prodrug which is converted to a substantially cytotoxic drug by the action of NQO2 in the manufacture of a medicament for treating a human patient with a target cell to be destroyed wherein the patient has been, is being or will be administered NRH or an analogue thereof which can pass reducing equivalents to NQO2.

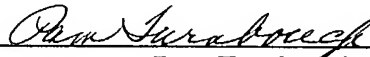
39. A kit of parts comprising a means for determining whether a target cell to be treated expresses NQO2 and NRH or an analogue thereof which can pass reducing equivalents to NQO2.

40. (Amended) The method of claim 29 wherein the patient has cancer.

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**CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.10**

I hereby certify that this paper and any documents referred to as attached or enclosed are being deposited with the United States Postal Service on this date, March 13, 2002, in an envelope as "Express Mail Post Office to Addressee" service under 37 C.F.R. § 1.10, Express Mail Label No. EL 778 572 141 US, addressed to Box Patent Application, Commissioner of Patents and Trademarks, Washington, D.C. 20231.

  
Pam Turnbough

Date: March 13, 2002

ATL1 #508691 v1

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**Pursuant to 37 C.F.R. § 1.121(b)(1)(iii)**





## THERAPEUTIC SYSTEMS

### CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of pending prior application Serial No. 09/445,865 filed February 11, 2000, entitled "*Therapeutic Systems*", by Philip John Burke and Richard John Knox, which is a 371 of International Application No. PCT/GB98/01731 filed in the United Kingdom Receiving Office for the Patent Cooperation Treaty on June 15, 1998, which claims priority to British application No. GB9712370.7 filed on June 14, 1997.

The present invention relates to therapeutic systems, particularly therapeutic systems for activating prodrugs and for the use of such systems in killing target cells, particularly tumour cells.

The delivery of a cytotoxic agent to the site of tumour cells is much desired because systemic administration of these agents can result in the killing of normal cells within the body as well as the tumour cells. The resulting toxicity to normal cells limits the dose of the cytotoxic agent and thus reduces the therapeutic potential of these agents. However, in some instances the administered agent has no intrinsic activity but is converted *in vivo* at the appropriate time or place to the active drug. Such analogues are referred to as prodrugs and are used extensively in medicine [Connors and Knox, 1995]. Conversion of the prodrug to the active form can take place by a number of mechanisms depending, for example, on changes of pH, oxygen tension, temperature or salt concentration or by spontaneous decomposition of the drug or internal ring opening or cyclisation.

WO 88/07378 describes a two-component system, and therapeutic uses thereof, wherein a first component comprises an antibody fragment capable of binding with a tumour-associated antigen and an enzyme

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WO 88/07378 describes a two-component system, and therapeutic uses thereof, wherein a first component comprises an antibody fragment capable of binding with a tumour-associated antigen and an enzyme capable of converting a pro-drug into a cytotoxic drug, and a second